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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
SINGH, ANOOP KUMAR	
ART UNIT	**PAPER NUMBER**
1632	

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Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/637,710	PANDA ET AL.	
	Examiner	Art Unit	
	Anoop Singh	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 September 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1 and 4* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1 and 4* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicants' amendments to the specification and claims filed on September 20, 2007 has been received and entered. Claims 2-3, 6 and 5-21 have been canceled. Claims 1 and 4 are pending in this application.

Election/Restrictions

Applicant's election of invention of claims 1-8 (group I) in the reply filed on May 2, 2006 was acknowledged. Because applicant did not specifically point out the supposed errors in the restriction requirement, the election was treated as an election without traverse (MPEP § 818.03(a)).

Claims 1 and 4 are under consideration in the instant application.

Specification

The objection to disclosure for containing an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of amendments to the specification removing hyperlink.

Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Claims 1 and 4 remain rejected under 35 U.S.C. 101 because the claimed invention is not supported by either a specific, substantial and credible asserted utility or a well-established utility.

Applicants argue that the specification establishes a role of melanopsin in light input and teaches that the attenuation in phase shifting in the claimed animals is a direct result of reduced sensitivity of the photic input pathway to light. It is also noted by applicants that they need not provide evidence that establishes that an asserted utility is a statistical certainty. Instead, the evidence is sufficient if, considered as a whole, it leads a person of ordinary skill in the art to conclude that the asserted utility is more likely than not true (MPEP 2170.02.VII). Applicants argue the evidence as a whole suggests that one of skill would be more likely than not to believe that melanopsin knockout mice would be useful for evaluating the effects of compounds on light sensitivity of the photic input pathway (pages 4 and 5 of the argument). Applicants also argue that observation that other genes may play in modulating light input (Beaule et al art of record) does not negate the utility of the invention. Applicants also cite Hattar et al and experiments in the specification that uses claimed knockout that also lacks functional rods and cones exhibit a complete loss of photic response (see page 6 and 7). Applicants assert that melanopsin knockout mouse also have utility in laboratory setting as a research tool for studies involving sensitivity of phototic pathways of light, which is substantial, creditable and real world utility.

In response, it is noted that claimed invention is directed to a transgenic knockout mouse whose genome comprises a homozygous disruption of endogenous melanopsin gene, where such disruption prevents the expression of a functional melanopsin protein in the cells of the mouse and mouse exhibits an attenuated circadian rhythm phase-shift in response to light pulse during dark portion of environmental dark/light cycle. Examiner would agree with applicant's assertion that claimed Opn4$^{-/-}$ mice shows no detectable defect in locomotor activity rhythms

when placed in constant darkness (Figure 2 A and B) and exhibit a significantly attenuated phase delay in comparison to the wild type animals (Figure 3). However, specification also teaches that the phase delay was significant at sub saturating irradiance of light, while only a slight attenuation of the phase shift was seen at higher irradiance in the knockout animals (pages 28-30 of the specification). This is further supported by Kumbalasiri et al (art of record, para. 372, col. 2, para. 2) who states "several labs that created melanopsin-null mice show that melanopsin-containing ipRGCs play a role in circadian photo -entrainment, ... and the photic regulation of the melatonin biosynthetic pathway. Many of the deficits in these responses were subtle or not apparent in melanopsin-null mice". Only after these mice were crossed with mice lacking functional rods and cones were extreme phenotypes observed. For example, transgenic mice lacking functional photoreceptors remain capable of regulating circadian locomotor activity by light in a manner indistinguishable from sighted controls. This ability to shift the phase of circadian activity rhythms in response to light pulses is attenuated in melanopsin-null mice. Interestingly, a residual capacity for light-induced phase shifting remains". Thus, in view of foregoing it appears that the phenotype of claimed mice lacking the melanopsin gene had normal enhancement of locomotion in the presence of dim lights but an impaired suppression of locomotion in the presence of bright light.

Applicants' argument of using claimed mouse in a laboratory setting as a research tool for studies involving sensitivity of photic pathways of light, (MPEP 2107.01) were fully considered but are not persuasive to the extent claimed mouse embrace an attenuated circadian rhythm phase shift in response to any light . Applicants cite MPEP 2107.01 in support of specific and substantial utility in laboratory setting. MPEP 2107.01 states

"Some confusion can result when one attempts to label certain types of inventions as not being capable of having a specific and substantial utility based on

the setting in which the invention is to be used. One example is inventions to be used in a research or laboratory setting. Many research tools such as gas chromatographs, screening assays, and nucleotide sequencing techniques have a clear, specific and unquestionable utility (e.g., they are useful in analyzing compounds). An assessment that focuses on whether an invention is useful only in a research setting thus does not address whether the invention is in fact "useful" in a patent sense. Instead, Office personnel must distinguish between inventions that have a specifically identified substantial utility and inventions whose asserted utility requires further research to identify or reasonably confirm. Labels such as "research tool," "intermediate" or "for research purposes" are not helpful in determining if an applicant has identified a specific and substantial utility for the invention."

In the instant case, the issue is not based on the setting such as a laboratory, in which the invention is to be used, rather analysis is based on whether claimed transgenic knockout mouse is used as research tool to perform further research to reasonably confirm and elucidate the role of melanopsin. The specification describes that Opn4.-/- mouse exhibit attenuation in light-induced phase resetting of the circadian oscillator, and a reduced papillary light reflex (PLR) under high irradiance levels, however, most non-visual photic responses in these mice remain largely intact. This suggests either the presence of additional inner retinal photoreceptors, or contributions from the outer retinal classical photoreceptors to non-visual photoresponses. The specification describe testing this hypothesis by generating mice deficient in both melanopsin and classical photoreceptors by breeding Opn4-/- mice with the C3H/HeJ mouse strain that carries the retinal degeneration (rd) mutation (see page 30, para. 106, figure 4, 5 and table 1). It is emphasized that examiner has previously cited references to indicate some degree of redundancy within the photoreceptive system and claimed mouse entraining normally to LD cycles, showing phase shifting in response to short light pulses, and manifest normal photic induction of clock genes in the SCN while under dim light, the magnitude of phase shifts is moderately reduced relative to wild-type animals. Given that resulting phenotype of a mouse is altered due to differences between mouse strain backgrounds, it appears one of skill in the art would have to

reasonably confirm the hypothesis as described in the instant application and by others in post filing art using rod-cone system. It is emphasized that inventions whose asserted utility requires further research to identify or reasonably confirm is not substantial utility.

In addition, it is noted that reference of Hattar et al (2003, art of record) used by applicant's in support of enablement cites Lucas et al (see ref. 8) that discloses melnopsin (*mop-/-*) knockout mice provides conclusive evidence that melanopsin is an indispensable component of a photoreceptive system with genuine physiological functions. The "precise role of melanopsin in the RGC phototransduction process, however, remains uncertain". It may be the photopigment of the intrinsically photosensitive RGCs, or it may perform some other function critical to their photosensitivity (Lucas, Science, 2003, see page 247, col. 1, last para.). Thus, it is apparent from the fore going discussion that in spite of melanopsin being indispensable component of a photoreceptive system with some physiological function, its precise role in phototransduction process was not elucidated at the time of filing of this application. Examiner would agree with applicants' assertion of using claimed knockout mouse as research tool for specific and substantial utility if a reasonable specific utility of claimed transgenic mouse is presented that shows an attenuated circadian rhythm phase shift in response to any light as embraced by the breadth of the claims. It is noted that applicants' supplied art (Hattar et al 2003, art of record) and other experiments in the specification confirmed the phenotype of claimed mouse in response to a light only after these mice are crossed with mice lacking functional rods and cones which would essentially result in different product (page 372, col.2, last para. citing Hattar et al 2003 and Panda et al 2003) and requires further research to identify or reasonably confirm the claimed subject matter. (see MPEP 2107.01).

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1 and 4 remain rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

As an initial matter, it is noted that examiner has inadvertently stated at one instance that claims 1 and 4 do not recite any phenotype (page 9, para.2.), In fact through out the rejection examiner has considered transgenic knockout having disclosed phenotype as evidenced by discussion on page 9, para 1 and subsequent discussion on nexus between observed phenotype and enabled use of the claimed invention (see response to arguments, pages 14-15).

Applicants argue that instant specification unambiguously demonstrates that melanopsin plays a role in light-sensitive photic input pathways and that one of skill could generate and use the claimed melanopsin-null mice (see page 9 of the specification).

In response, it is noted that examiner agrees with the applicant's assertion that claimed transgenic mouse satisfies the how to make prong of the enablement, thus, the only remaining issue is how one of skilled in the art would use the claimed product. In the instant case, instant specification and post filing art teaches that claimed invention of melanopsin knockout mice entrain normally to LD cycles, show phase shifting in response to short light pulses, and manifest normal photic induction of clock genes in the SCN. However, under dim light, the magnitude of phase shifts is moderately reduced relative to wild-type animals supra). Although, pre and post filing art summarized by the references of Beaule et al (Journal of

Molecular Neuroscience, 2003, 73-89, art of record), Kavakli et al (Mol Interv. 2002 Dec;2(8):484-92, art of record) and Kumbalsiri e al (2005, art of record, pages 371, col.2, last para bridging to page 372, col. 1, para. 1) contemplated the role of melanopsin in the phase shift of circadian rhythm in response to light and attenuation of the circadian rhythm phase shift in response to light pulses in melanopsin-null mice. Interestingly, art also teaches that a residual capacity for light-induced phase shifting remains. It is noted that only mice lacking functional rods and cones and null for melanopsin are completely incapable light-induced phase shifts (page 373, col. 1, para. 1). In the instant case, specification contemplates using claimed transgenic knockout mouse in a method for identifying a therapeutic agent for modulating circadian rhythm in a mammal by administering an agent or identifying the modulator of circadian rhythm on transgenic knockout animals that are useful for preventing or treating a number of conditions including advancing or delaying the phase of certain circadian rhythms in humans, insomnia, delayed-sleep phase syndrome, Irregular Sleep/Wake Pattern, advanced sleep phase syndrome, time zone change syndrome, winter depression, or other forms of depression; Alzheimer's disease, dementia, and anxiety (see paragraph 54 of the specification). The specification discloses alterations of response in the knockout mouse of the invention could indicate that the agent acts on a melanopsin-specific signal transduction pathway. Furthermore observation by Kumbalasiri et al and Kavakli it would be reasonable to state that phenotype seen in the transgenic knockout mouse of the invention may be compensated by another gene. In fact, Kavakli cite Ruby et al that teaches ops4-/- transgenic knockout mouse similar to one claimed in the instant application that assesses multiple measures of circadian function in these knockout mice to show that melanopsin is not essential for entrainment. Ruby et al states, "However, phase and period responses of melanopsin-deficient mice were about 40% less than in wild-type animals. Ruby concluded that melanopsin appears to be a significant contributor to

circadian function. Melanopsin may function as a photopigment, but it is also possible that it is critical for some other photopigment to perform normally. For example, it might serve as a retinaldehyde isomerase, like some other members of the opsin family. As with all knockout studies, the absence of a functional protein may trigger compensation during development or it may alter functioning of the adult system". Examiner would agree that specification and post filing art does show that mouse lacking functional rods and cones and null for melanopsin are completely incapable light-induced phase shifts suggesting potential role of melanopsin, however, disclosure provided guidance in terms of deletion of melanopsin gene failed to provide guidance in terms of its functional involvement in genus of disorder or its relationship to a condition associated with any of the disorder that could be treated by any therapeutic agent identified. In addition, post-filing art of Hattar et al and instant specification describes a transgenic mouse that is crossed with mouse that lack rods and cones to confirm the phenotype, are thus, not embraced by the scope of the claims. Therefore, because an artisan does not know how to use claimed product in any screening assay or disease or modulators of circadian rhythm, it would require undue experimentation for an artisan to first establish a link between the transgenic knockout animal with a specific condition or disease or generate other transgenic mouse (rod- cone and melanopsin null) and then test reversal of phase shift in response to any light in screening methods. Given that the specification and art does not disclose if the instant mice represent a model for a disease or condition associated with plurality of different disorders as described in the specification. An artisan would have to do further experimentation to establish the nexus between the phenotype seen in the mouse showing an attenuated circadian rhythm phase shift in a specific light pulse during dark portion of dark/light cycle to a disease or condition. In view of foregoing discussion, it is apparent that an artisan would have to perform undue experimentation to make use of the invention with out reasonable expectation of success.

It is noted that additional evidence establishing link between observed phenotype of claimed transgenic knockout mouse to a disease model or condition described in the specification in a way as to enable one skilled in the art to make use of the invention without undue experimentation may obviate the basis of this rejection.

Conclusion

No Claims allowed.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure: Hattar et al *Science* 295, 1065 (2002); Provencio et al (The Journal of Neuroscience, 2000, 20(2): 600-605), Capecchi (US patent no. 5,464,764, November 7, 1995) and Genebank number GenBank Accession Number AF_147789, dated 1/15/2000).

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Anoop Singh whose telephone number is (571) 272-3306. The examiner can normally be reached on 9:00AM-5:30PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Peter Paras can be reached on (571) 272- 4517. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Anoop Singh, Ph. D
Examiner, AU 1632

/Thaian N. Ton/
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